

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	1935	thrombin adj inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:35			0
2	BRS	L2	107	(thrombin adj inhibitor) same prodrug	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:35			0
3	BRS	L3	2	kit same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:43			0
4	BRS	L4	0	(pharmaceutical adj composition) same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:45			0
5	BRS	L5	21	melagatran	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:43			0
6	BRS	L6	6	melagatran same prodrug	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:44			0
7	BRS	L7	2	6 same (kit or composition)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:44			0
8	BRS	L8	1	(composition) same 2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:45			0
9	BRS	L9	5	((thrombin adj inhibitor) same prodrug ) or (melagatran same prodrug)) same (composition or formulation)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:46			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	2	kit same ((thrombin adj inhibitor) same prodrug )	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:56			0
2	BRS	L2	107	((thrombin adj inhibitor) same prodrug	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:56			0
3	BRS	L3	6	melagatran same prodrug	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:57			0
4	BRS	L4	5299	(venous adj thrombosis) or (pulmonary adj embolism) or (disseminated adj intravascular adj coagulation)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:58			0
5	BRS	L5	1	4 same (2 or 3)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/2 4 16:58			0

=> d his

(FILE 'HOME' ENTERED AT 16:48:24 ON 24 NOV 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA'  
ENTERED AT

16:48:53 ON 24 NOV 2002

L1 10243 S THROMBIN INHIBITOR

L2 50 S L1 (P) PRODRUG

L3 0 S L2 (P) (KIT OR COMPOSITION)

L4 29 S MELAGATRAN (P) PRODRUG

L5 1 S L4 (P) (KIT OR COMPOSITION OR FORMULATION)

L6 309321 S THROMBOSIS OR (PULMONARY EMBOLISM) OR  
(DISSEMINATED INTRAVASC

L7 14 S L6 (P) (L2 OR L4)

L8 9 DUPLICATE REMOVE L7 (5 DUPLICATES REMOVED)

=> log y

FILE 'HOME' ENTERED AT 16:48:24 ON 24 NOV 2002

=> file medline caplus biosis embase scisearch agricola

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 16:48:53 ON 24 NOV 2002

FILE 'CAPLUS' ENTERED AT 16:48:53 ON 24 NOV 2002

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FILE 'EMBASE' ENTERED AT 16:48:53 ON 24 NOV 2002

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FILE 'SCISEARCH' ENTERED AT 16:48:53 ON 24 NOV 2002

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FILE 'AGRICOLA' ENTERED AT 16:48:53 ON 24 NOV 2002

=> s thrombin inhibitor

L1 10243 THROMBIN INHIBITOR

=> s l1 (p) prodrug

L2 50 L1 (P) PRODRUG

=> s l2 (p) (kit or composition)

L3 0 L2 (P) (KIT OR COMPOSITION)

=> s melagatran (p) prodrug

L4 29 MELAGATRAN (P) PRODRUG

=> s l4 (p) (kit or composition or formulation)

L5 1 L4 (P) (KIT OR COMPOSITION OR FORMULATION)

=> d l5 1 ibib abs

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:772474 CAPLUS

DOCUMENT NUMBER: 133:340244

TITLE: A pharmaceutical formulation comprising a low molecular weight thrombin inhibitor and its prodrug

INVENTOR(S): Gustafsson, David

PATENT ASSIGNEE(S): Astrazeneca AB, Swed.

SOURCE: PCT Int. Appl., 30 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000064470	A1	20001102	WO 2000-SE756	20000419
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
SE 9901442	A	20001022	SE 1999-1442	19990421
BR 2000009847	A	20020108	BR 2000-9847	20000419

EP 1200118            A1    20020502            EP 2000-928047    20000419  
R: AT, BE, CH, DE, D    ES, FR, GB, GR, IT, LI, LU, NL    E, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL  
NO 2001005107        A    20011019            NO 2001-5107        20011019  
PRIORITY APPLN. INFO.:            SE 1999-1442        A    19990421  
                                 SE 1999-4419        A    19991203  
                                 WO 2000-SE756        W    20000419

OTHER SOURCE(S):            MARPAT 133:340244

AB    A pharmaceutical    \*\*\*formulation\*\*\*    contains a low mol. wt. thrombin inhibitor, or a pharmaceutically acceptable deriv. with an adjuvant, diluent or carrier; a pharmaceutical    \*\*\*formulation\*\*\*    including a \*\*\*prodrug\*\*\*    of a low mol. wt. thrombin inhibitor, or a deriv. of that \*\*\*prodrug\*\*\* , in admixt. with an adjuvant, diluent or carrier. The \*\*\*formulation\*\*\*    is suitable for administration in the treatment of a condition in which the inhibition of thrombin is required. A controlled, randomized, parallel group, Swedish multi-center pilot study was carried out. The study was open with regard to the drugs under evaluation but was blind for the patients, all personnel at the study sites, and for the person monitoring the expts. with regard to the doses of \*\*\*melagatran\*\*\*    and the \*\*\*prodrug\*\*\*    of    \*\*\*melagatran\*\*\* , EtOOC-CH<sub>2</sub>-(R)Cgl-Aze-Pab-OH (I). A combination of s.c. administered \*\*\*melagatran\*\*\*    and orally administered I is effective in preventing venous thrombosis after orthopedic surgery.

REFERENCE COUNT:            4            THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT.

=> d his

(FILE 'HOME' ENTERED AT 16:48:24 ON 24 NOV 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 16:48:53 ON 24 NOV 2002

L1            10243 S THROMBIN INHIBITOR  
L2            50 S L1 (P) PRODRUG  
L3            0 S L2 (P) (KIT OR COMPOSITION)  
L4            29 S MELAGATRAN (P) PRODRUG  
L5            1 S L4 (P) (KIT OR COMPOSITION OR FORMULATION)

=> s thrombosis or (pulmonary embolism) or (disseminated intravascular coagulation)  
L6            309321 THROMBOSIS OR (PULMONARY EMBOLISM) OR (DISSEMINATED INTRAVASCULAR COAGULATION)

=> s L6 (p) (l2 or l4)  
L7            14 L6 (P) (L2 OR L4)

=> duplicate remove l7  
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'  
KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n  
PROCESSING COMPLETED FOR L7  
L8            9 DUPLICATE REMOVE L7 (5 DUPLICATES REMOVED)

=> d l8 1-9 ibib abs

L8    ANSWER 1 OF 9    CAPLUS    COPYRIGHT 2002 ACS  
ACCESSION NUMBER:            2002:879541    CAPLUS  
TITLE:                      Oral-direct thrombin inhibitors  
AUTHOR(S):                  Crowther, Mark A.  
CORPORATE SOURCE:            McMaster University, Hamilton, ON, Can.  
SOURCE:                      Fundamental and Clinical Cardiology (2003), 46(New Therapeutic Agents in Thrombosis and Thrombolysis (2nd Edition)), 265-271  
                                 CODEN: FCCAEH; ISSN: 1067-5264  
PUBLISHER:                    Marcel Dekker, Inc.  
DOCUMENT TYPE:                Journal  
LANGUAGE:                      English

AB    Current strategies for the treatment and prevention of venous \*\*\*thrombosis\*\*\*    require a mix of parenteral and oral therapies that frequently require lab. monitoring. Oral-direct    \*\*\*thrombin\*\*\*    \*\*\*inhibitors\*\*\*    have the potential to simplify antithrombotic therapy; these agents produce a predictable anticoagulant response so that lab. monitoring may be unnecessary. Ximelagatran, the oral direct

\*\*\*thrombin\*\*\* \*\*\*inhibitor\*\*\* in the most advanced stage of development, is a \*\*\*prodrug\*\*\* of \*\*\*ximelagatran\*\*\* an active-site-directed inhibitor of thrombin. In phase II studies, ximelagatran has been evaluated as thromboprophylaxis in patients undergoing elective hip or knee replacement surgery and in patients with nonvalvular atrial fibrillation. The drug has also been studied in patients with acute venous \*\*\*thrombosis\*\*\*. In each case, ximelagatran appears to be at least as safe and effective as current antithrombotic interventions. Phase III studies with ximelagatran for these indications are currently underway. If ximelagatran lives up to its initial promise, it has the potential to revolutionize the prevention and treatment of \*\*\*thrombosis\*\*\*.

L8 ANSWER 2 OF 9 MEDLINE  
ACCESSION NUMBER: 2002416506 MEDLINE  
DOCUMENT NUMBER: 22161009 PubMed ID: 12170516  
TITLE: [Prophylaxis of postoperative thromboembolism. New alternatives to low-molecular-weight heparin]. Profylax mot postoperativ tromboembolism. Nya alternativ till lagmolekylart heparin.  
AUTHOR: Bergqvist David; Siegbahn Agneta  
CORPORATE SOURCE: Avdelningen for klinisk kemi, Akademiska sjukhuset, Uppsala.. david.bergqvist@kirurgi.uu.se  
SOURCE: LAKARTIDNINGEN, (2002 Jul 11) 99 (28-29) 3039-41. Journal code: 0027707. ISSN: 0023-7205.  
PUB. COUNTRY: Sweden  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: Swedish  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200209  
ENTRY DATE: Entered STN: 20020813  
Last Updated on STN: 20020914  
Entered Medline: 20020913

AB For somewhat more than a decade low molecular weight heparins have dominated in the pharmacological prevention of postoperative venous thromboembolism. At present there are some new methods of potential interest both as prophylactic substances but also to better understand the pathophysiology of deep vein \*\*\*thrombosis\*\*\*. These are inhibition of factor VII a/tissue factor complex (NAP, Nematode Anticoagulant Protein), inhibition of activated factor X (the synthetic pentasaccharide fondaparinux) and thrombin inhibition ( \*\*\*ximelagatran\*\*\* and its oral \*\*\*prodrug\*\*\* ximelagatran). They have been shown to be effective in high risk orthopaedic surgery. They have to show their place in the prophylactic arsenal in comparison with low molecular weight heparins (effect, safety, mode of administration, cost-effectiveness).

L8 ANSWER 3 OF 9 MEDLINE DUPLICATE 1  
ACCESSION NUMBER: 2002388952 IN-PROCESS  
DOCUMENT NUMBER: 22132572 PubMed ID: 12137410  
TITLE: BIBR-1048 Boehringer Ingelheim.  
AUTHOR: Mungall Dennis  
CORPORATE SOURCE: The Miami Project to Cure Paralysis, Department of Neurological Surgery, University of Miami School of Medicine, Lois Pope Life Center, FL 33101, USA.. Thertch@aol.com  
SOURCE: Curr Opin Investig Drugs, (2002 Jun) 3 (6) 905-7. Journal code: 100965718. ISSN: 1472-4472.  
PUB. COUNTRY: England: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals  
ENTRY DATE: Entered STN: 20020725  
Last Updated on STN: 20020725

AB BIBR-1048, a \*\*\*thrombin\*\*\* \*\*\*inhibitor\*\*\* and an orally-active \*\*\*prodrug\*\*\* of BIBR-953ZW, is under development by Boehringer Ingelheim as a potential antithrombotic agent [331881]. By 1999, BIBR-1048 was in phase II clinical trials for thromboembolism and the prevention of stroke due to atrial fibrillation [331881]; by April 2002, proof-of-principle had been demonstrated in phase II trials in deep vein \*\*\*thrombosis\*\*\* [446554]. In July 2001, the company revealed that an IND was expected to be filed for BIBR-953ZW in 2002 [415884].

L8 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2001:154 CAPLUS  
DOCUMENT NUMBER: 135:371637  
TITLE: Synthesis of thiochromane derivatives for use as  
thrombin inhibitors  
INVENTOR(S): Andersson, Kjell; Inghardt, Tord; Karlsson, Olle;  
Linschoten, Marcel; Nystroem, Jan-erik; Sundén, Gunnel  
PATENT ASSIGNEE(S): Astrazeneca AB, Swed.  
SOURCE: PCT Int. Appl., 93 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001087879	A1	20011122	WO 2001-SE1052	20010514

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,  
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,  
UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: SE 2000-1803 A 20000516  
OTHER SOURCE(S): MARPAT 135:371637  
GI

/ Structure 1 in file .gra /

AB Synthesis of thiochromane derivs. (I) (R1 = halo; R2 = H, halo, alkoxy; Y  
= S=O, SO2) for use as \*\*\*thrombin\*\*\* \*\*\*inhibitors\*\*\* is  
disclosed. Thus, I (R1 = Cl, R2 = H, Y = SO2) (II) is prepd. in 8 steps  
from 4-chloro-2-methoxythiophenol, Et bromopropanoate and  
paraamidinobenzylamino azetidinecarboxylate. II in thrombin clotting time  
assay shows an IC50TT of > 0.05.upsilon.M. I are useful as  
\*\*\*prodrugs\*\*\*, competitive inhibitors of trypsinlike proteases, such as  
thrombin, and in particular in the treatment of conditions where  
inhibitors of thrombin is required (e.g. \*\*\*thrombosis\*\*\* ) or as  
anticoagulants.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 9 MEDLINE DUPLICATE 2  
ACCESSION NUMBER: 2001301777 MEDLINE  
DOCUMENT NUMBER: 21127175 PubMed ID: 11228340  
TITLE: The direct thrombin inhibitor melagatran and its oral  
prodrug H 376/95: intestinal absorption properties,  
biochemical and pharmacodynamic effects.  
AUTHOR: Gustafsson D; Nystrom J; Carlsson S; Bredberg U; Eriksson  
U; Gyzander E; Elg M; Antonsson T; Hoffmann K; Ungell A;  
Sorensen H; Nagard S; Abrahamsson A; Bylund R  
CORPORATE SOURCE: Department of Cardiovascular Pharmacology, AstraZeneca R&D  
Molndal, S-431 83, Molndal, Sweden..  
david.gustafsson@astrazeneca.com  
SOURCE: THROMBOSIS RESEARCH, (2001 Feb 1) 101 (3) 171-81.  
Journal code: 0326377. ISSN: 0049-3848.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200105  
ENTRY DATE: Entered STN: 20010604  
Last Updated on STN: 20010604  
Entered Medline: 20010531

AB Suboptimal gastrointestinal absorption is a problem for many direct  
\*\*\*thrombin\*\*\* \*\*\*inhibitors\*\*\*. The studies presented herein

describe the new oral direct \*\*\*thrombin\*\*\* \*\*\*inhibitor\*\*\* H 376/95, a \*\*\*prodrug\*\*\* with two protecting residues added to the direct \*\*\*thrombin\*\*\* \*\*\*inhibitor\*\*\* \*\*\*melagatran\*\*\*. Absorption properties in vitro: H 376/95 is uncharged at intestinal pH while \*\*\*melagatran\*\*\* is charged. H 376/95 is 170 times more lipophilic (octanol water partition coefficient) than \*\*\*melagatran\*\*\*. As a result, the permeability coefficient across cultured epithelial Caco-2 cells is 80 times higher for H 376/95 than for melagatran. Pharmacokinetic studies in healthy volunteers: H 376/95 is converted to \*\*\*melagatran\*\*\* in man. Oral bioavailability, measured as \*\*\*melagatran\*\*\* in plasma, is about 20% after oral administration of H 376/95, which is 2.7-5.5 times higher than after oral administration of \*\*\*melagatran\*\*\*. The variability in the area under the drug plasma concentration vs. time curve (AUC) is much smaller with oral H 376/95 (coefficient of variation 20%) than with oral \*\*\*melagatran\*\*\* (coefficient of variation 38%). Pharmacodynamic properties: H 376/95 is inactive towards human alpha-thrombin compared with \*\*\*melagatran\*\*\* [inhibition constant (K(i)) ratio, 185 times], a potential advantage for patients with silent gastrointestinal bleeding. In an experimental \*\*\*thrombosis\*\*\* model in the rat, oral H 376/95 was more effective than the subcutaneous low molecular weight heparin dalteparin in preventing \*\*\*thrombosis\*\*\*. Conclusion: By the use of the \*\*\*prodrug\*\*\* principle, H 376/95 endows the direct \*\*\*thrombin\*\*\* \*\*\*inhibitor\*\*\* \*\*\*melagatran\*\*\* with pharmacokinetic properties required for oral administration without compromising the promising pharmacodynamic properties of \*\*\*melagatran\*\*\*.

L8 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:772474 CAPLUS

DOCUMENT NUMBER: 133:340244

TITLE: A pharmaceutical formulation comprising a low molecular weight thrombin inhibitor and its prodrug

INVENTOR(S): Gustafsson, David

PATENT ASSIGNEE(S): Astrazeneca AB, Swed.

SOURCE: PCT Int. Appl., 30 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000064470	A1	20001102	WO 2000-SE756	20000419
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
SE 9901442	A	20001022	SE 1999-1442	19990421
BR 2000009847	A	20020108	BR 2000-9847	20000419
EP 1200118	A1	20020502	EP 2000-928047	20000419
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
NO 2001005107	A	20011019	NO 2001-5107	20011019
PRIORITY APPLN. INFO.:				
			SE 1999-1442	A 19990421
			SE 1999-4419	A 19991203
			WO 2000-SE756	W 20000419

OTHER SOURCE(S): MARPAT 133:340244

AB A pharmaceutical formulation contains a low mol. wt. \*\*\*thrombin\*\*\* \*\*\*inhibitor\*\*\*, or a pharmaceutically acceptable deriv. with an adjuvant, diluent or carrier; a pharmaceutical formulation including a \*\*\*prodrug\*\*\* of a low mol. wt. \*\*\*thrombin\*\*\* \*\*\*inhibitor\*\*\*, or a deriv. of that \*\*\*prodrug\*\*\*, in admixt. with an adjuvant, diluent or carrier. The formulation is suitable for administration in the treatment of a condition in which the inhibition of thrombin is required. A controlled, randomized, parallel group, Swedish multi-center pilot study was carried out. The study was open with regard to the drugs under

evaluation but was blind for the patients, all personnel at the study sites, and for the person monitoring the expts. with regard to the doses of \*\*\*melagatran\*\*\* and the \*\*\*prodrug\*\*\* of \*\*\*melagatran\*\*\*, EtOOC-CH<sub>2</sub>-(R)Cgl-Aze-Pab-OH (I). A combination of s.c. administered \*\*\*melagatran\*\*\* and orally administered I is effective in preventing venous \*\*\*thrombosis\*\*\* after orthopedic surgery.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:742118 CAPLUS  
DOCUMENT NUMBER: 133:310144  
TITLE: Preparation of amidine-terminated peptides as prodrugs of thrombin inhibitors  
INVENTOR(S): Baucke, Dorit; Mack, Helmut; Seitz, Werner; Hornberger, Wilfried; Backfisch, Gisela; Delzer, Jorgen  
PATENT ASSIGNEE(S): BASF A.-G., Germany  
SOURCE: PCT Int. Appl., 136 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: German  
FAMILY ACC. NUM. COUNT: 4  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061609	A2	20001019	WO 2000-EP3009	20000405
WO 2000061609	A3	20010315		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1165601	A2	20020102	EP 2000-920661	20000405
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
BR 2000009674	A	20020115	BR 2000-9674	20000405
NO 2001004875	A	20011113	NO 2001-4875	20011008
PRIORITY APPLN. INFO.:			DE 1999-19915930 A	19990409
			DE 1999-19934123 A	19990723
			DE 1999-19947920 A	19991006
			WO 2000-EP3009 W	20000405

OTHER SOURCE(S): MARPAT 133:310144  
GI

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The invention concerns prepn. of title compds., e.g. (I), which act as prodrugs for competitive inhibitors of trypsin-type serin proteases, esp. thrombin and kininogenases such as kallikrein, for use in treatment of disease or as thrombin inhibitors, anticoagulants and anti-inflammatory agents. Extensive examples of prepn. of precursors, e.g. (II) or (III), are given. In in vitro tests of oral resorption rate using human colon adenocarcinoma cells grown on polycarbonate membranes, I had very good transport characteristics. Substances were also tested in rats for effect on ecarin clotting times, activated partial thromboplastin times, and thrombin times (no data).

L8 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:742090 CAPLUS  
DOCUMENT NUMBER: 133:296664  
TITLE: Preparation of peptide amidine analogs as prodrugs of thrombin inhibitors  
INVENTOR(S): Baucke, Dorit; Mack, Helmut; Seitz, Werner;

Hornberger, Wilfried; Backfisch, Gisela; Delzer, Jurg  
PATENT ASSIGNEE(S): BASF A.-G., Germany  
SOURCE: PCT Int. Appl., 72 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: German  
FAMILY ACC. NUM. COUNT: 4  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061577	A1	20001019	WO 2000-EP3008	20000405
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000009653	A	20020108	BR 2000-9653	20000405
EP 1169318	A1	20020109	EP 2000-915197	20000405
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001004807	A	20011204	NO 2001-4807	20011003
PRIORITY APPLN. INFO.:				
			DE 1999-19915930 A	19990409
			DE 2000-10006799 A	20000215
			WO 2000-EP3008 W	20000405

OTHER SOURCE(S): MARPAT 133:296664  
GI

/ Structure 2 in file .gra /

AB The present invention relates to prodrugs of general formula (I) (see document for definitions), useful as prodrugs with improved adsorption for in vivo compds. which are competitive inhibitors of trypsin-like serine proteases, esp. thrombin. Thus, reacting N-(CH<sub>2</sub>C(O)OC(CH<sub>3</sub>)<sub>3</sub>)(C(O)OC(CH<sub>3</sub>)<sub>3</sub>)-D-cyclohexylalanine (prepn. given) and 3,4-dehydro-L-proline Me ester hydrochloride led to an intermediate which, following a previous Patent synthesis (WO 96/25326), was converted to the cyano precursor of (II), which was reacted with H<sub>2</sub>NOH and NH<sub>3</sub>, to give the hydroxyamidine compd. In in vitro transport expts., II showed very good transport. In in vivo pharmacokinetic tests using rats and dogs, the compds. themselves had poor thrombin-inhibiting action, but acted as prodrugs which, through metab., led to active compds. (no data).

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 1997:506597 CAPLUS  
DOCUMENT NUMBER: 127:136080  
TITLE: Preparation of peptide derivatives as prodrugs of thrombin inhibitors  
INVENTOR(S): Antonsson, Thomas; Gustafsson, David; Hoffmann, Kurt-Jurgen; Nystrom, Jan-Erik; Sorensen, Henrik; Sellen, Mikael  
PATENT ASSIGNEE(S): Astra Aktiebolag, Swed.; Antonsson, Thomas; Gustafsson, David; Hoffmann, Kurt-Jurgen; Nystrom, Jan-Erik; Sorensen, Henrik; Sellen, Mikael  
SOURCE: PCT Int. Appl., 94 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 9723499	A1	19970703	WO 1996-SE1680	19961217
W: AL, AM, AT, AU, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9610353	A	19970623	ZA 1996-10353	19961209
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AU 706350	B2	19990617		
EP 869966	A1	19981014	EP 1996-943446	19961217
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CN 1209139	A	19990224	CN 1996-180024	19961217
BR 9612148	A	19990713	BR 1996-12148	19961217
JP 2000504313	T2	20000411	JP 1997-523571	19961217
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EP 995755	A1	20000426	EP 1999-120315	19961217
EP 995755	B1	20010816		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001089498	A2	20010403	JP 2000-220423	19961217
AT 204292	E	20010915	AT 1999-120315	19961217
RU 2176644	C2	20011210	RU 1998-111148	19961217
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NO 9802809	A	19980820	NO 1998-2809	19980618
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PRIORITY APPLN. INFO.:

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US 1997-776231	A1	19970131
US 1999-353644	A1	19990715
US 2000-708449	B1	20001109

OTHER SOURCE(S): MARPAT 127:136080

AB Title compds. of formula R1O(O)C-CH2-(R)Cgl-Aze-Pab-R2 [wherein R1 = H, C1-10 alkyl, (un)substituted C1-3 alkylphenyl, A1C(O)N(R3)R4, A1C(O)OR3; (R)Cgl = (R)-cyclohexyl glycine; Aze = (S)-azetidine-2-carboxylic acid; Pab = 1-amidino-4-aminomethylbenzene; R2 (which replaces one of the hydrogen atoms in the amidino unit of Pab) = OH, OC(O)R5, C(O)OR6, C(O)OCH(R7)OC(O)R8; R3 and R4 are independently e.g., H, C1-6 alkyl, Ph, or together with the nitrogen atom represent pyrrolidinyl or piperidinyl; R5 = C1-17 alkyl, Ph, or 2-naphthyl (all of which are optionally substituted by C1-6 alkyl or halogen); R6 = (un)substituted 2-naphthyl, Ph, C1-3 alkylphenyl, C1-12 alkyl; R7 = H, C1-4 alkyl; R8 = e.g., 2-naphthyl, Ph, C1-6 alkoxy, (un)substituted C1-8 alkyl] or a pharmaceutically acceptable salt thereof, which are useful as prodrugs of inhibitors of trypsin-like proteases (no data), such as thrombin, and in particular in the treatment of conditions where inhibition of thrombin is required (e.g. thrombosis) or as anticoagulants, were prepd. For example, EtO2C-CH2-(R)Cgl-Aze-Pab-COOCH2CH:CH2 was prepd. via coupling of Me3CO2C-(R)Cgl-Aze-Pab-H with allyl chloroformate followed by Boc deprotection and coupling with Et bromoacetate. The title compds. were all found to exhibit oral and/or parenteral bioavailability in rats as the active inhibitor HO2C-CH2-(R)Cgl-Aze-Pab-H, either as the free acid and/or as one or more ester thereof.

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(FILE 'HOME' ENTERED AT 16:48:24 ON 24 NOV 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 16:48:53 ON 24 NOV 2002

L1 10243 S THROMBIN INHIBITOR  
L2 50 S L1 (P) PRODRUG

L3 0 S L2 (P) (KIT OR COMPOSITION)  
L4 29 S MELAGATRAN (PRODRUG)  
L5 1 S L4 (P) (KIT OR COMPOSITION OR FORMULATION)  
L6 309321 S THROMBOSIS OR (PULMONARY EMBOLISM) OR (DISSEMINATED INTRAVASC  
L7 14 S L6 (P) (L2 OR L4)  
L8 9 DUPLICATE REMOVE L7 (5 DUPLICATES REMOVED)

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COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	48.11	48.32
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-4.34	-4.34

STN INTERNATIONAL LOGOFF AT 16:54:07 ON 24 NOV 2002